Estimating in vivo drug release from a new theophylline Compritol® 888 ATO matrix formulation using appropriate biorelevant test methods

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ABSTRACT SUMMARY

The present series of test focused on evaluating the robustness of drug release from lipid based theophylline matrix tablets under a simulated fasted gastrointestinal passage. A robust sustained release was observed in all experiments.

INTRODUCTION

Oral extended-release (ER) dosage forms have represented a broad segment of research and development in the pharmaceutical industry for many years. Housing drugs with a short half-life they can typically enable a reduced dosing frequency which comes along with various potential advantages such as e.g. reduced fluctuations in drug levels, a reduced total amount of drug that has to be used, improved patient compliance, better and more uniform clinical effects, lower incidence of side effects.

Since drug absorption from ER dosage forms is governed by the rate of release from the formulation and since these formulations typically contain much higher drug doses than the respective immediate-release (IR) formulations, it is essential to assure robust and reproducible *in vivo* drug release to prevent the unwanted toxic peaks and sub-therapeutic troughs in plasma levels caused by “dose dumping” or insufficient/hindered drug release.

Matrix-based formulations, consisting of the active drug embedded in a polymer matrix which controls drug release, have traditionally been the most commonly used ER dosage forms. Traditionally, a whole range of water-soluble or water-swellabe polymers with high molecular weight with HPMC being the most representative candidate have been used as matrix formers. However, some of these formulations have shown increased sensitivity to the composition of gastrointestinal fluids and gastrointestinal shear forces [1-2] which could not be predicted by standard dissolution experiments in the paddle or basket apparatus.

To predict whether the ER dosage form meets its *in vivo* release profile goals, one needs to apply an adequate release test system that reflects conditions relevant to the *in vivo* conditions of drug release.

The aim of the present set of experiments was evaluate the robustness of lipid based theophylline matrix tablets in various biorelevant dissolution test devices simulating passage through the human gastrointestinal (GI) tract. Compritol® 888 ATO (glyceryl dibehenate, NF), the matrix former, is a fine white powder composed of spherical particles with a mean particle diameter of 50µm. It has excellent tabletting properties and is chemically inert and neutral in flavor. With a low HLB of 1 and a high melting point (70°C) it has proven utility in the production of an insoluble and non-swellable matrix which sustains drug release principally by a mechanism of diffusion.

EXPERIMENTAL METHODS

Materials

Theostat® L.P. 100 mg, lot # G00405 (Pierre Fabre Medicament, Boulogne, France) was obtained by prescription, Theophylline, Compritol® 888 ATO, dicalcium phosphate anhydrate (DCPA, Fujicalin®), lactose monohydrate, silicon dioxide (Aerosil® 200), Mg alumino metasilicate (Neusilin® US2) and magnesium stearate used for manufacturing the tablets as well as sodium chloride, hydrochloric acid conc., sodium dihydrogen phosphate, sodium hydroxide and acetic acid used to prepare the release media were all of analytical grade and purchased commercially.

Tablet preparation

100 mg theophylline, Compritol® 888 ATO and diluents were sieved through a 810 µm mesh, blended, subsequently lubricated and compressed using a single punch excenter press (14 mm, Korsch EK03). The total tablet weight was 600mg.

Table 1: Composition of theophylline matrix tablets containing Compritol® 888 ATO.

Ingredient	%
Theophylline	16.7
Compritol® 888 ATO	15.0
Dicalcium phosphate anhydrate (DCPA, Fujicalin®)	42.9
Lactose	21.4
Magnesium alumino metasilicate (Neusilin® US2)	3.0
Magnesium stearate	1.0

Dissolution test setup

Dissolution studies were performed at 37°°C with a) the reciprocating cylinder apparatus, (USP III; ERWEKA RRT 10: 200 mL per vessel, 420 µm mesh screens, 10 dpm), b) the flow through apparatus (USP IV; ERWEKA DFZ: 22.6 mm cell filled with 1 mm-size glass beads, Whatman® glass fiber filter (GF/F), tablets on holder, flow rates: stomach: 8 mL/min, small intestine and colon: 4 mL/min), and c) an ERWEKA biorelevant dissolution stress test apparatus intended to reflect phases of pressure waves simulating episodes of high gastrointestinal motility (gastric emptying (GE), ileocecal passage (ICP)) and phases of transport (780 mL, 100 rpm, 3 pressure waves (300 mbar) for gastric emptying and ileocecal passage, 1 min rotation at 100 rpm every 10 min for intestinal transport events). Results in USP III and IV were performed in the buffer media, whereas in the stress test experiments both buffers and the corresponding biorelevant media (with bile compounds) were used. Media and corresponding residence times are given in Table 2

Table 2: Dissolution media [3] and corresponding residence times

GI section	Medium	pH	Residence
Stomach	SGF / FaSSGF	1.8	60 min
Small intestine	(Blank) FaSSIF	6.8	240 min
Proximal colon	SCoF	5.8	240 min
Colon	Blank FaSSIF	6.5	180 min

RESULTS AND DISCUSSION

Results from the experiments simulating a fasted gastrointestinal passage of monolithic dosage forms show slight differences in the release profile which is most likely due to the nature of the apparatus and the test settings which are likely to result in different hydrodynamic conditions. Overall, both the Theostat® L.P. 100 mg marketed product and the theophylline Compritol® 888 ATO matrix formulation are neither sensitive towards the changing pH-conditions (Figures 1-3), nor are significantly affected by biorelevant gastrointestinal stress conditions in the fasted GI tract (Figures 3 and 4).

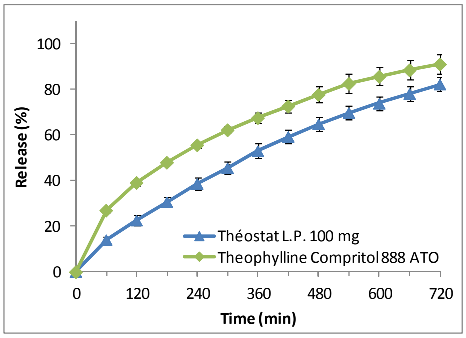

Figure 1: Theophylline release from different tablets under simulated fasted conditions in the reciprocating cylinder apparatus equipped with buffer media (mean of n = 3, ± SD)

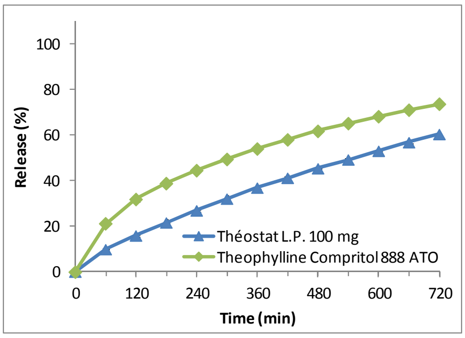

Figure 2: Theophylline release from different tablets under simulated fasted conditions in the flow through apparatus equipped with buffer media (mean of n = 3, ± SD)

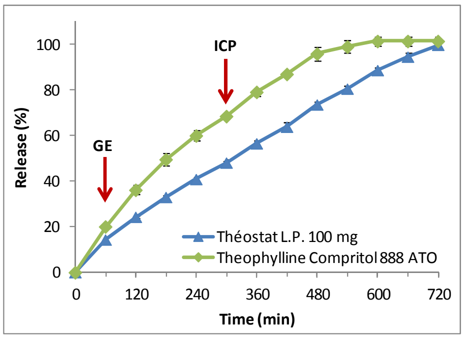

Figure 3: Theophylline release from different tablets under simulated fasted conditions in the biorelevant stress test apparatus equipped with buffer media (mean of n = 3, ± SD)

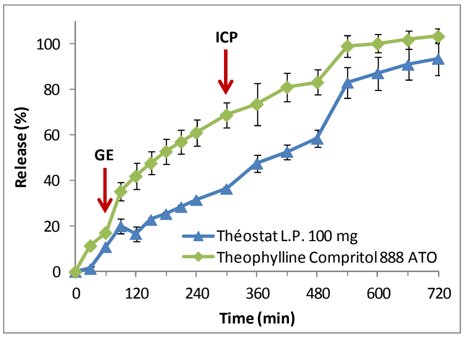

Figure 4: Theophylline release from different tablets under simulated fasted conditions in the biorelevant stress test apparatus equipped with biorelevant media (mean of n = 3, ± SD)

CONCLUSION

Compritol® 888 matrix tablets prepared by direct compression offer a quite robust sustained release in biorelevant fasted conditions even when exposed to simulated mechanical stress in the fasted human GIT. Further studies should be carried out in fed conditions - which exert a significant role in drug dose dumping.

REFERENCES

1. Klein, S. Dissolution Technologies, 2009. **16**(3): 28-40.
2. Garbacz, G., et al. AAPS PharmSciTech, 2013.
3. Klein, S. AAPS Journal, 2010. **12**(3): 397-406.